The relationship of pre-operative laboratory coagulation parameters with post-operative hemorrhage in neurosurgical patients

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Dedication

This thesis is dedicated to the faculty of the Department of Neurosurgery at the University of Minnesota. Without the support of the entire department, this work would not have been possible.

Abstract

Background: Neurosurgeons are frequently asked to operate on patients with blood clotting abnormalities. During the last twenty years, the use of NSAIDs has skyrocketed. Patients taking ASA and NSAIDs are routinely asked to stop these medications before an elective operation. INR is a widely used measure of the extrinsic pathway of coagulation. The INR value at which neurosurgeons are willing to proceed with elective surgical procedures is not grounded in strong evidence. The principal objective of this study is to determine the relationship between preoperative coagulation status (as measured by objective laboratory tests) and the rate of clinically significant central nervous system hemorrhage after neurosurgical procedures

Methods: This is a retrospective case-control study of operative neurosurgical patients from the University of Minnesota Medical Center from 2003 to 2009. Within this group of 3698 operative cases there were 44 cases of post-operative hemorrhage.

Results: The overall rate of hemorrhage during this period was 1.2%. After adjusting for procedure class the odds having a hemorrhage increased by 73.4% as INR increased by 0.1 unit (p=0.0062) The total N for the final model was 174, representing exclusion of 28 patients who did not have complete records

Discussion: Patients suffering a hemorrhage within 30 days of operation were more likely to have had an elevated INR than control patients. While values such as INR are used to assess the coagulation cascade, we have seen that many other factors are purported to contribute to post-operative hemorrhage. These potential confounding factors were collected and evaluated in this study. The results of our series support the idea that, by further refining the ability to predict risk of postoperative hemorrhage, a prospectively collected cohort of neurosurgical patients and their risk factors for post-operative hemorrhage could make a significant contribution to the safe practice of neurosurgery.

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BACKGROUND:

Neurosurgeons are frequently asked to operate on patients with blood clotting abnormalities. These have varying causes, which include genetic (ex. hemophilia) and iatrogenic (therapeutic manipulation of the blood-clotting cascade in patients with a prosthetic heart valve, atrial fibrillation, or history of stroke or myocardial infarction) factors. Due to advances in the care of heart disease and stroke, countless patients are maintained on aspirin for primary or secondary prophylaxis against these vascular events. A recent survey conducted by Pignone et al showed 41% of respondents over the age of 40 affirming the use of ASA for cardiovascular disease prevention.[i] During the last twenty years, the use of NSAIDs has skyrocketed as their indications continue to expand. A 2002 study published in JAMA showed that within the previous thirty days 17% of ambulatory patients above the age of 18 had used ASA, an additional 17% had used ibuprofen, and 3.5% had used naproxen.[ii]

Patients taking ASA and NSAIDs are routinely asked to stop these medications anywhere from 7 to 14 days before operation. A large systematic review and meta-analysis in the cardiothoracic surgery literature showed a significant increase in bleeding complications in those patients receiving ASA within seven days of surgery.[iii] Within neurosurgical literature, a 1994 paper suggested an increased risk of hematoma in patients receiving ASA, dipyridamole, or NSAIDs within fourteen days of surgery.[iv] This study was a five-year review of the cases from one neurologic center in the United Kingdom. This would classify the study as level 4 evidence according to the Oxford Centre for Evidence-based Medicine Levels of Evidence.[v]

In elective cases for patients on warfarin, the International Normalized Ratio (INR) is brought back to "normal" levels in an appropriate manner before the operation. INR is a widely used measure of the extrinsic pathway of coagulation. It serves to standardize the prothrombin time

(PT) measurements of individuals by taking into account the sensitivity of a particular batch of tissue factor used in the determination of the PT. The INR is the ratio of the patient's PT to a control sample. The level at which neurosurgeons are willing to proceed with elective surgical procedures is, as would be expected, quite variable and not grounded in strong evidence regarding the association of abnormal laboratory clotting values with the rate of intra- and post-operative hemorrhage. The routine laboratory screening of surgical patients for bleeding disorders is controversial. Eckman et al concluded that for surgical patients without synthetic liver dysfunction or a history of oral anticoagulant use there was no benefit in routine laboratory testing of bleeding risk.[vi] This study did not include neurosurgical patients.

Still other situations demand immediate action, for to delay the evacuation of a symptomatic posterior fossa hemorrhage may lead to irreversible neurologic injury or death. A neurosurgeon may be called to the bone marrow transplant unit of his or her hospital, and confronted with a patient with signs of mass effect in the posterior fossa, an INR of 5.2 and a platelet count of 17,000. Because of the immunocompromised status of the patient, any blood product will need to be irradiated before transfusion – making the wait time now measured in hours instead of minutes. These elective and urgent scenarios are a source of concern and disagreement among clinicians. Reliable determination of the relationship between laboratory clotting measures and hemorrhagic complications is needed.

The principal objective of this study is to determine the relationship between preoperative coagulation status (as measured by objective laboratory tests) and the rate of clinically significant central nervous system hemorrhage after neurosurgical procedures. In addition to examining the risk associated with abnormalities in coagulation tests, and because reliable laboratory

assessments of the effect on coagulation of antiplatelet agents do not exist, we examined the effect of preoperative exposure to antiplatelet agents and looked for a difference between urgent and elective operations.

Our principal hypothesis is that the incidence of a clinically significant postoperative hemorrhage is higher (relative to the roughly 1% postoperative hemorrhage rate quoted in the neurosurgical literature) in patients with a preexisting abnormality of INR, aPTT, or platelet count when compared to patients with laboratory values within the 'normal' range. Our secondary hypotheses are as follows: 1) the rate of clinically significant postoperative hemorrhage is not higher in patients undergoing urgent procedures than in patients undergoing elective neurosurgical procedures, 2) the rate of clinically significant postoperative hemorrhage is not higher in patients taking aspirin, clopidogrel, or non-steroidal anti-inflammatory drugs (NSAIDs) preoperatively.

METHODS:

This is a retrospective case-control study using medical records of operative neurosurgical patients from the University of Minnesota Medical Center. We reviewed the surgical records and 'Morbidity and Mortality' conference proceedings dating back to the year 2003 to identify potential cases and controls. Prior to 2003 the electronic medical record at our institution was in limited use and data was therefore spread over a combination of paper and electronic inpatient and outpatient charts.

In order to estimate the required sample size for this study, we reviewed literature on the rate of postoperative hemorrhage after neurosurgical procedures. Palmer et al, in their 5-year series found a 1.1% rate of postoperative hematoma (71 hematomas out of 6668 operative cases).

Taylor et al looked at hematoma rates after 2305 intracranial procedures and found a rate of 2.2%.[vii] There have been other studies with varying results. The review by Seifman et al found a wide range (0.8-50%) of hemorrhage rates after intracranial surgery.[viii] Sample size estimates were based on 80% power to detect the odds ratio per 0.2 unit increase in INR as statistically significant at a level of 0.05. The standard deviation of INR within the matched cases and controls was estimated to be 0.07. The ratio of cases to controls was set to 1:4. We constructed Table 1 to determine the odds ratio that could be detected based upon the number of cases of post-operative hemorrhage that could be identified and characterized from our surgical records. Cases were defined as patients who suffered a clinically significant post-operative hemorrhage in the thirty days following neurosurgical procedures. For the purposes of this study, we have defined clinically significant hemorrhage as that which prompts at least one of the following: (1) new neurologic deficit not directly related to surgical procedure, (2) return to the operating room, (3) prolongation of hospital stay for monitoring or rehabilitation purposes, (4) discharge to facility other than home due to one of the above (i.e. nursing home, rehab center).

The following information was gathered from the charts for both cases and controls: DOB, gender, date of operation, pre-operative INR, aPTT, and platelet count, timing of procedure (Elective/Urgent), CPT code, surname of attending surgeon (treated as a categorical variable), pre-operative anti-platelet exposure within 14 days of surgery (True/False), post-operative anticoagulation therapy (True/False). All collected laboratory values were within thirty days of surgery. In the case where a lab was drawn multiple times in the thirty days prior to surgery, the lab value closest to the start of the operation was used.

Nurses in the pre-operative holding area who routinely review current medications with patients on the morning of surgery identified preoperative antiplatelet exposure. We reviewed these

records and noted any use of ASA, NSAIDs or other anti-platelet drugs within 14 days of surgery. This form includes a space for recording the date of last dose. Post-operative anticoagulation was declared positive when there was any record of chemical anticoagulation being given during the acute, inpatient post-operative stay. This included warfarin, heparin, or low-molecular-weight heparins (LMWH).

We used the CPT code to stratify procedures into one of three categories; (1) craniotomy or craniectomy, (2) burr holes (EVD placement, brain biopsy, shunt or neurostiumulator placement), (3) spine/[carotid] endarterectomy/peripheral nerve. The goal was to categorize procedures broadly according to the level and nature of their invasiveness. Category 1 involves removing a portion of the skull, with or without replacement. Category 2 involves a small hole in the skull and passage of some small catheter or probe through the brain parenchyma, and category 3 involves exposure of neural elements or critical neurovascular structures outside the skull.

The cases and controls were matched on date-of-birth (+/- 3 years), gender, and date of operation (+/- 2 years). The database containing pertinent information from the cases and possible controls (all other operated patients during this period) was accessed using an algorithm in SAS 9.1.3 (SAS Institute Inc., Cary, NC) statistical software to identify multiple matches for each case based upon the aforementioned criteria. In cases where more than four possible matches were identified, the first four were taken. When four or fewer matches were identified, all of these matches were used as controls for that particular case. The medical record numbers are assigned sequentially, and so assigning controls in this manner could introduce a bias in favor of selecting controls from earlier years. This study covered a six-year period, during which time practice did not change significantly. We therefore believed this risk of bias was relatively small in the present study.

Statistical Methods:

Descriptive statistics were calculated to summarize cases and controls' characteristics. Frequencies and proportions were calculated for categorical variables. Means, standard deviations, medians, and ranges were computed for continuous variables. Since this is a matched case-control study, conditional logistic regression was used to investigate the relationship between the outcome of being a case and the covariates. The analysis began with the full model, which includes all core variables and all potential confounders. Confounders were then removed one-at-a-time in the order of least significance (largest p-value). Statistical analysis was performed with SAS 9.1.3 (SAS Institute Inc., Cary, NC) statistical software. A p-value <0.05 was considered statistically significant. Our final model included 40 cases and 134 controls (ratio of 1:3.4).

RESULTS:

We identified 3698 operative procedures performed between 2003 and 2009. Within this group there were 43 cases of post-operative hemorrhage within 30 days of operation. The overall rate of hemorrhage during this period was 1.2%. Our final statistical model excluded 4 patients with hemorrhage due to incomplete records. Table 2 provides a description of the patients included in the final statistical model.

After adjusting for aPTT, platelet, and procedure class, the patients who suffered a post-operative hemorrhage were more likely to have presented with an elevated INR (i.e. to have been "exposed" to a higher INR within the 30 days preceding their surgical procedure). The odds of

hemorrhage increased by 43% for each increase of 0.1 in the INR value. This did not reach the level of statistical significance at the 0.05 level (p=0.095). INR, aPTT, and platelets were left in with each step of this model – regardless of p-value. This was done because these were the main variables of interest that we wished to investigate in relation to post-operative hemorrhage. At no time during this model did aPTT or platelet count approach significance. A second model was then performed in the same manner that excluded aPTT and platelet count. After adjusting for procedure class in the final model, the odds of having a hemorrhage increases by 73.4% as INR increases by 0.1 unit (p=0.0062). See Table 3.

The range of INR values seen in this study was 0.72 to 1.71. The total N for the final model was 174, representing exclusion of 28 patients who did not have complete records. The statistical analysis (conditional logistic regression) requires all data fields to be complete in order to use that record, but in the excluded patients one or more pieces of data could not be ascertained after full review of all electronic and paper medical records. 24 of these exclusions were in the control group. Bias cannot be excluded, given that 4 cases (4/44 or 9%) were in the hemorrhage group. We did not see any significant differences in the demographics of the excluded patients in comparison with those included in this study.

Urgent versus elective status did not rise to statistical significance at any time and was eliminated from the model. We also sought to determine if preoperative use of ASA, NSAIDs, or clopidogrel were independent predictors of hemorrhage. None of these variables contributed significantly to the risk of hemorrhage in this population. We identified several possible confounders and examined these in our statistical modeling. Factors included surgeon, and procedure type. There were no models in which these were found to have a statistically significant relationship to ‘case’ or ‘control’ status.

DISCUSSION:

In this case control study we found that patients suffering a hemorrhage within 30 days of operation were more likely to have had an elevated INR than control patients who did not suffer postoperative hemorrhage. A case-control study cannot estimate the incidence of an event (post-operative hemorrhage in our case), but it can indirectly estimate the ratio of incidences between groups. Our overall hemorrhage rate among the surgical cases performed during this interval was 1.2%. This figure is comparable to other published series.

While a case-control study is retrospective, and proportions are fixed, the determined odds ratio can provide a reasonable estimate of relative risk in certain situations. One specific criterion for such a situation is a very low incidence. The reported rate of post-operative hemorrhage after neurosurgery is typically reported to be around 1-2%. A second important factor is that the extrapolation must not be made to data outside the range found in the study, hence our described odds ratios would only be valid up to an INR of 1.7. The odds ratio of being exposed to a higher INR among cases suggests that this laboratory value can aid in the risk assessment for post-operative hemorrhage.

While values such as INR are used to assess the coagulation cascade, we have seen that many other factors are purported to contribute to post-operative hemorrhage. These potential confounding factors were collected and evaluated in this study. We narrowed neurosurgical operations down into three broad categories for the purposes of statistical modeling and to investigate a potential difference in hemorrhage rates among variably invasive procedures. The

three classes [craniotomy/craniectomy; burr holes; extracranial] represent a broad way to categorize the type of procedure performed. See Table 4.

Craniotomy/craniectomy operations involve removing (with or without replacement) a portion of the skull. This class covers the most invasive operations that neurosurgeons perform. The craniotomy is the window through which neurosurgeons expose brain tumors, aneurysms, and other malformations of the brain. Craniectomy is currently performed most often to relieve malignant intracranial hypertension that can arise from various underlying causes (trauma, infarct, hemorrhage, tumor). The category of 'burr holes' includes procedures where there is minimal bony exposure to the brain (many burr holes are the size of a nickel and can be as small as a pencil) and often a catheter or probe passed through the parenchyma for varying purposes (ventricular shunt, deep brain stimulating electrodes, biopsy, parenchymal physiologic monitors). Extracranial procedures involve the spine, peripheral nerves and extracranial blood supply to the brain. While the spine is not technically encased completely in a fixed volume, its canal is not readily expansile and still vulnerable to small volumes of hematoma. The great vessels in the neck are similarly not contained in the bony skull, but a hematoma after surgery in this area can cause life-threatening problems with the patients' airway. In this study, we did not find a relationship between our pre-determined 'class' of operation and post-operative hemorrhage.

There is an emerging body of literature in transfusion medicine that suggests the risks of major bleeding in patients with and without abnormal pre-procedural laboratory values is equivocal. A 2005 review of the literature by Segal and Dzik[ix] identified 25 studies looking at this issue. The authors identify that most of these studies were small, retrospective and of generally poor formal quality with wide confidence intervals associated with their results. Nevertheless, they report that

these studies do not support that idea that an elevated INR is predictive of peri-procedural bleeding. Looking at the studies that make up this review, there is one key difference.

While these were identified as invasive procedures, they were not open surgical procedures. The studies looked at the following procedures (respectively): angiography, bronchoscopy, liver biopsy, liver laparoscopy, transjugular liver biopsy, para/thoracentesis, transjugular kidney biopsy, and kidney biopsy. Open neurosurgical procedures are clearly more invasive than these percutaneous procedures. Even the 'burr hole' class of neurosurgical procedures in our study involves passing catheters through brain parenchyma. As previously stated, a much smaller hematoma volume can cause significant clinical deficits in this area. While we do not dispute the findings as they relate to the studied procedures, we are concerned about the validity of extrapolating these results to neurosurgery.

The recent availability of anticoagulants that do not require monitoring of coagulation times (ex. direct thrombin inhibitors) is a cause for real concern among neurosurgeons. If the level of anticoagulation does predict postoperative hemorrhage risk, and relatively small elevations of INR are associated with substantial increase in risk, the absence of a predictive measurement of the degree of anticoagulation will make neurosurgical decision-making in these patients more difficult and could result in avoidable and potentially devastating postoperative hemorrhage.

Case control studies are useful first steps when investigating potentially causal factors for a rare event. It should be noted that one retrospective study cannot legitimately claim that any causal relationship exists between a laboratory test and a post-operative hemorrhage. The results of our series support the idea that, by further refining the ability to predict risk of postoperative hemorrhage based on preoperative laboratory evaluation of the coagulation system, a

prospectively collected cohort of neurosurgical patients and their risk factors for post-operative hemorrhage could make a significant contribution to the body of knowledge in this field and to the safe practice of neurosurgery.

Table 1. Required sample sizes for selected odds ratio detection

Odds ratio per 0.2 unit increase in INR that could be detected	# of cases required	# of controls required
2.5	24	96
2	42	168
1.8	58	232
1.6	91	364

Table 2. Patients left in the final model where only INR and procedure class were included (N=174)

	Case (N=40)	Control (N=134)
Age		
N (Mean ± SD)	40 (52.7 ± 20.5)	134 (52 ± 20.3)
Gender		
Male	19 (47.5%)	65 (48.5%)
Female	21 (52.5%)	69 (51.5%)
Pre-operative INR (ref. range 0.86-1.14)		
N (Mean ± SD)	40 (1.1 ± 0.2)	134 (1 ± 0.1)
Pre-operative aPTT (ref range 22-37 sec)		
N (Mean ± SD)	39 (33.2 ± 14.7)	119 (29.3 ± 5)
Pre-operative platelet count (ref range 150-450)		
N (Mean ± SD)	40 (230 ± 92.1)	124 (245.9 ± 83.7)
Pre-operative exposure to ASA within 14 days		
True	13 (32.5%)	31 (23.1%)
False	27 (67.5%)	103 (76.9%)
Pre-operative exposure to NSAIDs within 14 days		
True	2 (5%)	10 (7.5%)
False	38 (95%)	124 (92.5%)
Pre-operative exposure to Plavix within 14 days		
True	1 (2.5%)	6 (4.5%)
False	39 (97.5%)	128 (95.5%)
Timing of procedure		
Elective	28 (70%)	118 (88.7%)
Urgent	12 (30%)	15 (11.3%)
Post operative anticoagulation		
True	9 (22.5%)	15 (11.2%)
False	31 (77.5%)	119 (88.8%)
Death due to hemorrhage		
True	4 (10%)	0
False	36 (90%)	134 (100%)

Table 3. Results of conditional logistic regression analysis (with platelets and aPTT excluded)

Effect	Odds Ratio (95% CI)	P value
Pre-operative INR (per 0.1 unit change)	1.7 (1.2, 2.6)	0.0062
Procedure class burr holes (EVD, biopsy, shunt) vs. spine/endarterectomy/peripheral nerve	1.5 (0.5, 4.4)	0.5427
Procedure class craniotomy/craniectomy vs. spine/endarterectomy/peripheral nerve	1.2 (0.5, 2.9)	0.9911

Table 4. Breakdown of procedures by category of all patients in the initial model (N=202)

Procedure Class	Cases	Controls
burr holes (EVD, biopsy, shunt, neurostimulator)	12 (30%)	28 (20.9%)
craniotomy/craniectomy	14 (35%)	48 (35.8%)
spine/endarterectomy/peripheral nerve	14 (35%)	58 (43.3%)

BIBLIOGRAPHY:

[i] Pignone M, Anderson GK, Binns K, Tilson HH, Weisman SM. Aspirin use among adults aged 40 and older in the United States: Results of a national survey. Am J Prev Med. 2007 May; 32(5): 403-7.

[ii] Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States: The slone survey. JAMA. 2002 Jan 16; 287(3):337-44.

[iii]Alghamdi AA, Moussa F, Fremes SE. Does the use of preoperative aspirin increase the risk of bleeding in patients undergoing coronary artery bypass grafting surgery? systematic review and meta-analysis. J Card Surg. 2007 May-Jun;22(3):247-56.

[iv] Palmer JD, Sparrow OC, Iannotti F. Postoperative hematoma: A 5-year survey and identification of avoidable risk factors. Neurosurgery. 1994 Dec;35(6):1061,4; discussion 1064-5.

[v] OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

[vi] Eckman MH, Erban JK, Singh SK, Kao GS. Screening for the risk for bleeding or thrombosis. Ann Intern Med. 2003 Feb 4;138(3):W15-24.

[v]Taylor WA, Thomas NW, Wellings JA, Bell BA. Timing of postoperative intracranial hematoma development and implications for the best use of neurosurgical intensive care. J Neurosurg. 1995 Jan;82(1):48-50.

[vi]Marc A. Seifman, Phillip M. Lewis, Jeffrey V. Rosenfeld, Peter Y. K. Hwang. (2011) Postoperative intracranial haemorrhage: a review. *Neurosurgical Review* . Online publication date: 19-Jan-2011.

[vii]Segal JB, Dzik WH; Transfusion Medicine/Hemostasis Clinical Trials Network. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review. Transfusion. 2005 Sep;45(9):1413-25.